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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/960,612 | 09/20/2001 | Christen M. Anderson | 660088.446 | 5657 |

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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

| EXAMINER | |
|---|---|
| HUI, SAN MING R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/960,612 | Applicant(s) ANDERSON ET AL. | |
|---|---|---|---|
| | Examiner San-ming Hui | Art Unit 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *12-26 and 35-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9,12* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

## DETAILED ACTION

The amendments filed January 2, 2003 have been entered.

Claims 1-40 are pending.

Claims 12-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

Claims 22-26, 35-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected specie, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

The claims have been examined herein to the extent they read on the elected invention and species.

This application contains claims 12-26 and 35-40 are drawn to an invention and specie nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The outstanding rejection of claim 9 with regard to the lack of antecedent basis under 35 USC 112, second paragraph is withdrawn in view of the amendments filed January 2, 2003.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Cpd. of formula No. I, does not reasonably provide enablement for other mitochondrial Na+/Ca2+ exchanger antiporters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines "mitochondrial Na+/Ca2+ exchanger antiporters". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "mitochondrial Na+/Ca2+ exchanger antiporters" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. The instant claims read on all "mitochondrial Na+/Ca2+ exchanger antiporter(s)", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

***Response to the arguments with regard to the rejection under 35 USC 112, first paragraph***

The Examiner would like to apologize the oversight of citing compounds of Formula No. I (Roman numerical) as Cpd. No. 1 and apologize any confusion that may be caused by the oversight. The correction is made herein. The compounds of Formula No. I (Roman numerical) are considered enabled in the instant invention.

Applicant's arguments filed January 2, 2003 averring enough guidance and disclosure is disclosed in the instant specification have been considered but are not found persuasive. Even though the mitochrondrial Na+/Ca+ transport activities are well-

known, it does not automatically enable one of skilled in the art to have possession of compounds that possesses the structural/functional characteristics for the specific claimed activities. In other words, applicants merely describe what applicants want the compounds to do, but not the actual compounds themselves through a recitation of functional language, i.e., an agent that can impairs the mitochrondrial calcium/sodium antiporter (MCA) activities. Attention is directed to *General Electric Company v. Wabash Appliance Corporation et al* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed: "the vice of a functional claim exists not only when a claims is "wholly" functional, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty". Functional language at the point of novelty, as herein employed by Applicants, is further admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406: stating this usage does "little more than outlin[e] goals appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". Applicants functional language at the point of novelty fails to meet the requirements set forth under 35 USC 112, first paragraph. Claims employing functional language at the point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limits of the monopoly asserted" *General Electric Company v. Wabash Appliance Corporation et* supra, at 468. Claims thus constructed provide no guidance as to medicaments employed, levels for providing therapeutic benefit, or provide notice for those practicing

in the art, limits of protection. Simply stated, the presented claims are an invitation to experiment, not reciting a specific medicament regimen useful for practicing the instant invention.

Moreover, Examiner notes that the reasons is not whether one of skilled artisan would know how to measure or ascertain the MCA activities; but rather whether one of skilled artisan would be able to ascertain compounds possessed such activity without undue experimentation. As discussed above, the instant specification does not provide guidance that allows one of skilled artisan to practice the full scope of the instant invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "a subject having or suspected of being at risk for having diabetes mellitus" in claim 1 renders the claims indefinite as to the subject being treated herein. It is not clear who will be suspected of being at risk of having diabetes. Please note that applicant's arguments filed January 2, 2003 are drawn to the diagnostic criteria or risk factor assessment of diabetes. The instant claim encompasses subjects that are suspected to be at risk. For a subject to be in risk of having diabetes, he/she has to be diagnosed to have certain signs and symptoms. For a subject that is suspected to be at risk of having diabetes, no diagnosis is required to be made. Therefore, the metes and bounds of the claims are not clear.

The expression "agent that ... impairs mitochondrial calcium/sodium antiport activity" in claim 1 renders the claims indefinite as to the active compounds encompassed by the claims herein. It is not clear what compounds, other than the ones disclosed in the instant specifcation, would be considered as "agent that ... impairs mitochondrial calcium/sodium antiport activity".

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 and 27-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennedy et al. (J. Clin. Invest.,1996; 98(11):2524-2538 from IDS received January 4, 2002) and Cox and Matlib (Trends Pharmacol. Sci., 1993; 21(4):595-599 from IDS received January 4, 2002).

Kennedy et al. teaches insulin secretion as dependent upon cellular glucose levels and resultant elevation of cytosolic and intramitochondrial Ca2+ (See particularly the abstract). Kennedy et al. also teaches carbachol acts synergistically with glucose to increase both cytosolic and intramitochondrial Ca2+ and thereby increasing the secretion of insulin (See particularly page 2533, col. 2, last paragraph to page 2535, first). The skilled artisan would see the increase of insulin level in response to elevated glucose level as a treatment of diabetes.

Cox and Matlib teaches that the elected compound, CGP-37157, is a potent mitochondrial Na+/Ca2+ exchanger antagonist which would be expected to increase the intramitochondrial Ca2+ concentration (See page 10, Table 1 and page 409, col. 1, last paragraph).

The references do not expressly teach employing CGP-37157 orally in diabetes therapy.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the elected compound, CGP-37157, to treat diabetes.

One of ordinary skill in the art would have been motivated to administer the elected compound, CGP-37157, to treat diabetes. Based on the teachings of Kennedy, one of ordinary skill in the art would reasonably expect compounds, such as CGP-37157, increasing the intramitochondrial Ca2+ level in response to elevated glucose level to provide increased insulin and thereby treating diabetes, regardless of the active site of CGP-37157 might be. Since the insulin production is increased by the administration of CGP-37157, one of ordinary skill in the art would be reasonably expect the activities of CGP-37157 takes place in an insulin secreting cells, absent evidence to the contrary. The skilled of artisan would possess all conventional administration method of the active compounds such as oral administration. The selection of one or another route of administration would be seen as a simple selection from among obvious alternatives.

***Response to Arguments***

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant's arguments filed January 2, 2003 averring Kennedy not teaching MCA; and Cox not teaching MCA being manifested in insulin secreting cells. Both arguments have been considered but are not found persuasive. Kennedy discloses the relationship between intramitochrondrial calcium levels, glucose levels, and insulin secretion. With the increase of intramitochrondrial calcium levels, secretion of insulin is also increased. Cox teaches that the elected compound, CGP-37157, is useful to increase the intramitochrondrial calcium levels by blocking (i.e., impairing) the MCA activities. Therefore, employing agents that increase the intramitochondrial Ca2+ level in response to elevated glucose level to provide increased insulin, such as CGP-37157, and thereby treating diabetes would be reasonably expected to be useful.

In addressing the applicants' arguments with regard to Cox's teachings of MCA in cardiac tissue only, attention is directed to Gunter et al. (reference AH from IDS received January 2, 2003), which teaches $Na^+$-dependent calcium transport (MCA activity) dominates in heart, skeletal muscle, brain, and other tissues and the $Na^+$-independent transport dominates in lung and kidney because of the strong magnesium inhibition of $Na^+$-dependent mechanism in those tissue (See page 321, col. 1, second paragraph). Based on the teachings of Gunter, one of ordinary skill in the art would expect MCA activities would be present in any tissues except for tissue having strong

magnesium inhibition, such as lung and kidney. Therefore, the cited prior art, as a whole, would render the instant claims obvious, absent evidence to the contrary.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
April 3, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

4/9/03